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- (54) **Piperidine compounds and their preparation and use.**

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168922v, Columbus, Ohio, US; **S.D. BRINK-**
MAN et al.: "Measurement of cholinergic
drug effects on memory in Alzheimer's dis-
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Description

The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease.

Due to the in general improved health situation in the western world, elderly-related diseases are much more common now than in the past and are likely to be even more common in the future.

One of the elderly-related symptoms is a reduction of the cognitive functions. This symptom is especially pronounced in the pathological disease known as Alzheimer's disease. This disease is combined with, and also most likely caused by, a up to 90% degeneration of the muscarinic cholinergic neurons in nucleus basalis, which is part of substantia innominata. These neurons project to the prefrontal cortex and hippocampus and have a general stimulatory effect on the cognitive functions of the forebrain as well as of hippocampus, namely learning, association, consolidation, and recognition.

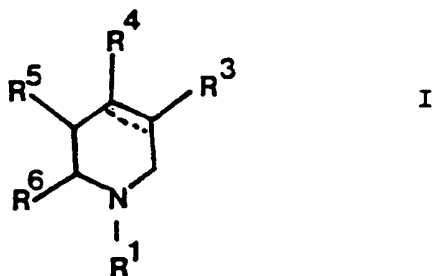
It is a characteristic of Alzheimer's disease that although the cholinergic neurons degenerate, then the postsynaptic muscarinic receptors in the forebrain and hippocampus still exist. Therefore muscarinic cholinergic agonists are useful in the treatment of Alzheimer's disease and in improving the cognitive functions of elderly people.

It is well known that arecoline (methyl 1-methyl-1,2,5,6-tetrahydropiperidine-3-carboxylate) is such a cholinergic agonist.

Arecoline however has a very short biological half life and a small separation between central and peripheral muscarinic effects. Furthermore arecoline is a rather toxic compound.

Accordingly it is the object of the invention to provide new muscarinic cholinergic compounds.

The compounds of the invention are piperidine compounds having the general formula I



wherein

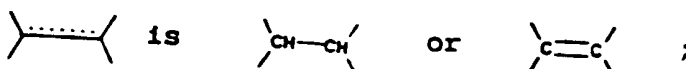
at least one of R^3 , R^4 , and R^5 is



and the other independently are H or C_{1-6} -alkyl,

wherein R' is H, C_{3-8} -alkyl, phenyl, thienyl, cyclopropyl, or C_{1-3} -alkoxymethyl; and

R^1 and R^6 independently are H or C_{1-6} -alkyl



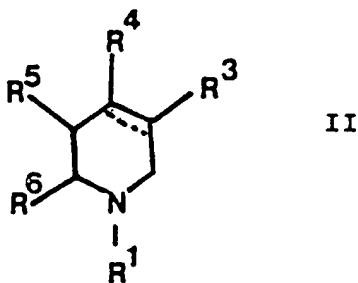
and salts thereof with a pharmaceutically-acceptable acid.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride,

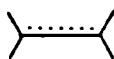
hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salt.

The invention also relates to a method of preparing the above mentioned compounds. This method comprises

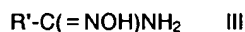
- 5 a) reacting a reactive derivative of a compound having the general formula II



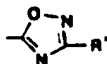
wherein R¹, R⁶, and



25 have the meanings defined above and wherein one of R³, R⁴ and R⁵ is CO₂H or a reactive derivative thereof, such as an ester, and the other independently are H or C₁₋₆-alkyl, with a compound having the general formula III

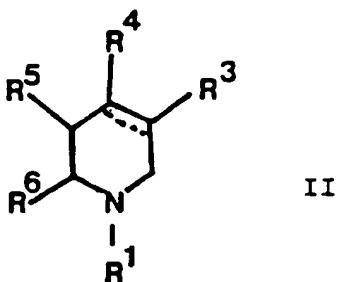


wherein R' has the meaning defined above to form a compound of the general formula I, wherein one of R³, R⁴ and R⁵ is

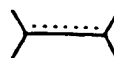


wherein R' has the meaning defined above,

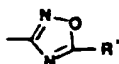
- 40 b) reacting a compound having the general formula II



wherein R¹, R⁶, and



have the meanings defined above and
 wherein one of R³, R⁴, and R⁵ is CN and the other independently are H or C₁₋₆-alkyl, with NH₂OH to
 form a compound having the general formula II wherein one of R³, R⁴, and R⁵ is C(=NOH)NH₂ and the
 other independently are H or C₁₋₆-alkyl, and reacting this compound with R'-COCl or (R'-CO)₂O to form
 a compound of formula I, wherein one of R³, R⁴, and R⁵ is



wherein R' has the meaning defined above.

The pharmacological properties of the compounds of the invention can be illustrated by determining
 their capability to inhibit the specific binding of ³H-QNB (³H-quinuclidinyl benzilate) by 50%. The inhibitory
 effect of a substance on ³H-QNB binding to brain membranes reflects the affinity of the substance for
 muscarinic acetylcholine receptors. (Yamamura, H.I. and Snyder, S.H., Proc.Natl.Acad.Sci. 71, 1725-29-
 (1979). The test is carried out as follows:

Fresh whole forebrain from male Wistar rats (200-250 g) is homogenized by an Ultra-Turrax homogen-
 izer (5-10 s) in volumes of 0.32 M sucrose. The homogenate is centrifuged at 4,300 x g for 5 min. The
 pellet is discarded and the supernatant centrifuged at 40,000 x g for 15 min. The final pellet is
 rehomogenized in 50 mM KH₂PO₄, pH 7.1 (1000 ml per g of original tissue) and this crude membrane
 preparation is used for binding assays. To 2.5 ml of tissue suspension is added 25μl of test solution* and
 25μl ³H-QNB (1 nM final concentration). Samples are thoroughly mixed and incubated at 37 ° C for 20 min.
 after incubation, samples are poured directly onto GF/C glass fiber filters under suction and immediately
 washed 2 times with 10 ml of buffer at 0 ° C. Non-specific binding is determined in duplicate using atropin
 (1μg/ml final concentration) as the test substance. The amounts of radioactivity on the filters are determined
 by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

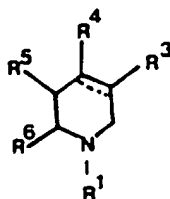
* Test compound is dissolved in 10 ml 96% ethanol (if necessary, acidified by 25μl 1N HCl and heated on a
 steambath for less than 5 min) at a concentration of 0.22 mg/ml. Three dilutions are made in 48% ethanol
 (1.1μg/ml, 11μg/ml and 110μg/ml). Concentrations of 10, 100 and 1000 ng/ml (final concentration) are
 added to duplicate assays. 25-75% inhibition of specific binding must be obtained, before calculation of
 IC₅₀.

The test value will be given as IC₅₀ (the concentration/μg/ml) of the test substance which inhibits the
 specific binding of ³H-QNB by 50%).

$$IC_{50} = (\text{applied test substance concentration}) \times \frac{1}{\left(\frac{C_0}{C_x} - 1\right)} \mu\text{g/ml}$$

where C₀ is specific binding in control assays and C_x is the specific binding in the test assay (the
 calculation assumes normal mass-action interaction).

Test results obtained by testing some compounds of the present invention will appear from the
 following table 1.

TABLE 1

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R^1	R^3	R^4	R^5	R^6		Inhibition in vitro QNB binding ($\mu\text{g/ml}$)
CH_3		H	H	H		2.0
CH_3		H	H	H		3.2
CH_3		H	H	H		4.9
H		H	H	H		4.7
CH_3		H	H	CH_3		3.3
CH_3	CO_2CH_3	H	H	H		21.0

50 The compound of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective muscarinic cholinergic agonistic amount of the active ingredient commensurate with the intended daily

dosage range to be employed. Tablets containing ten (10) mg of the active ingredient or, more broadly, one (1) to hundred (100) mg per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are conveniently unit dosages.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir of the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 1-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 1-100 mg/day, preferably 10-70 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tableting techniques contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel™	31.4 mg
Amberlite™ IRP 88	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

Due to the high muscarinic cholinergic receptor agonistic activity, the compounds of the invention are extremely useful in the treatment symptoms related to a reduction of the cognitive functions of the brain of mammals, when administered in an amount effective for stimulating the cognitive functions of the forebrain and hippocampus. The important stimulating activity of the compounds of the invention includes both activity against the pathological disease, Alzheimer's disease as well as against normal degeneration of brain function. The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of stimulation of the cognitive functions of the forebrain and hippocampus, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective forebrain and hippocampus stimulating amount, and in any event an amount which is effective for improving the cognitive function of mammals due to their muscarinic cholinergic receptor agonistic activity. Suitable dosage ranges are 1-100 mg daily, 10-100 mg daily, and especially 30-70 mg daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1

1-Methyl-3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

To a solution of sodium ethoxide, (prepared from sodium (180mg;7.8 mmol)), distilled ethanol (20ml), molecular sieves (5g), and methoxymethylcarboxamide oxime (832 mg;8 mmol) were added. The mixture

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was stirred at room temperature for 10 min whereafter arecoline, HBr (1,0g;4.23 mmol) was added. The mixture was heated at 80 °C for 12 h, filtered and evaporated in vacuo. To the residue was added water (10 ml) and the mixture was extracted with ether (3 x 25 ml). The combined extracts were dried (MgSO₄) and evaporated in vacuo. Upon dissolving the residue in ethanol (99.9%)(5 ml) a solution of oxalic acid (350 mg;3.9 mmol) in ethanol (99.9%)(10 ml) was added. Addition of ether gave an analytically pure product in a yield of 500 mg (40%). M.P. 153-154 °C.

EXAMPLE 2

10 (RS)-1-Methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

The compound was synthesized as described above in example 1 using cyclopropylcarboxamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the title compound in 42% yield. M.P. 108-109 °C.

EXAMPLE 3

1-Methyl-4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

20 The compound was synthesized as described above in example 2 using 1-methyl-4-ethoxycarbonyl-piperidinium chloride (Lambrecht and Mutschler, Arzneimittel Forsch.(Drug Res.) 23, 1427 (1973)) instead of dihydroarecoline. Crystallization gave the title compound in 50% yield. M.P. 168-169 °C.

EXAMPLE 4

25 1-Methyl-4-(3-propyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

The compound was synthesized as described above in example 3 using butanamide oxime. Crystallization gave the title compound in 33% yield. M.P. 117-118 °C.

EXAMPLE 5

30 1-Methyl-3-(3-propyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

35 The compound was synthesized as described above in example 1 using butanamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the title compound in 32% yield. M.P. 153-154 °C. yield. M.P. 168-169 °C.

EXAMPLE 6

40 1-Methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using cyclopropyl carboxamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the title compound in 34% yield. M.P. 169-172 °C.

EXAMPLE 7

50 1-Methyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using benzamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the title compound in 16% yield. M.P. 185-186 °C.

EXAMPLE 8

55 a: 1-Methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime

To a solution of sodium methoxide, prepared from sodium (575 mg; 25 mmol) in methanol (30 ml),

hydroxylamononium chloride (1,74g; 25 mmol) was added. The mixture was stirred at room temperature for 30 min and filtered. A solution of 1-methyl-3-cyano-1,2,5,6-tetrahydropyridine (Liberatore et al, Tetrahedron Letters 46, 4735, (1968)) (1,65 g; 13,5 mmol) in methanol (20 ml) was added to the filtrate. The reaction was stirred at room temperature for 20 h and evaporated. The residue was extracted with ethanol (50 ml),
 5 filtrated and evaporated to give the title compound in 25% yield.

b: 1-Methyl-3-(5-propyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

A solution of 1-methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime (200 mg; 1,29 mmol) in butyric anhydride (5 ml) was heated at 80 °C for 24 h. After evaporation in vacuo the residue was dissolved in 4N NaOH (5 ml) and extracted with ether (3 x 25 ml). The ether phases were dried (MgSO₄), filtered and evaporated in vacuo. The residue was dissolved in ethanol (99,9%)(5 ml) and added to a solution of oxalic acid (100 mg; 1,1 mmol) in ethanol (99,9%)(5 ml). Addition of ether gave the title compound in a yield of 65%. M.P. 170-171 °C.

EXAMPLE 9

1-Methyl-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

816mg(8.0mmol) of isopropylcarboxamide oxime was added to a solution of sodium ethoxide (7.8 mmol) in 20ml of distilled ethanol and 5g molecular sieves. The mixture was stirred at room temperature for 10 min whereafter 1.0g(4.23mmol) of arecoline, HBr was added. The mixture was heated at 80 °C for 12 h, filtered and evaporated in vacuo. 10ml of water was added to the residue and the mixture was extracted with ether (3 x 50 ml). The combined extracts were dried with MgSO₄ and evaporated in vacuo. The residue
 25 was dissolved in 5 ml of 99,9% ethanol and a solution of 380mg(4.23 mmol) of oxalic acid in 10 ml of 99,9% ethanol was added. Crystallization from ether gave the title compound in 37% yield. M.P. 133-134 °C.

EXAMPLE 10

1-Methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2, 5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 9 using pentanamide oxime instead of isopropylcarboxamide oxime. M.P. 121-123 °C.

EXAMPLE 11

3-(3-Propyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 9 using norarecoline, HCl and butanamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively. M.P. 162-163 °C.

The following compounds were synthesized in exactly the same way using pentanamide oxime, cyclopropylcarboxamide oxime and methoxymethylcarboxamide oxime, respectively.

3-(3-Butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6- tetrahydropyridinium oxalate. M.P. 207-208 °C.

3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate. M.P. 169-171 °C.

3-(3-Methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6- tetrahydropyridinium oxalate. M.P. 188-190 °C.

EXAMPLE 12

a. 1-Ethyl-3-methoxycarbonyl-1,2,5,6-tetrahydro-pyridinium chloride

0.509ml (6.2mmol) of ethyl iodide was added to a mixture of 1.0g(5.6mmol) norarecoline and 2.1g of potassium carbonate in 20ml of acetone. The reaction mixture was refluxed for 16 hours, filtered and evaporated in vacuo. The residue was dissolved in 10ml aqueous of 4N sodium hydroxide and was then
 55 extracted with ether (3 x 50 ml). The combined ether phases were dried with (MgSO₄), filtered and evaporated in vacuo. The residue was dissolved in methanol and 10ml of 2.3 N hydrogen chloride in ether was added. Crystallization with ether gave the title compound.

b. 1-Ethyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The title compound was synthesized as described in example 9 using 1-ethyl-3-methoxycarbonyl-1,2,5,6-tetrahydropyridinium chloride and pentanamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively.
 5 M.P. 102-104 °C.

EXAMPLE 1310 a. (RS)-3-Methoxycarbonyl-5-methyl-1,2,5,6-tetrahydropyridinium oxalate

A solution of (RS)-3-carboxy-5-methyl-1,2,5,6-tetrahydropyridinium bromide (Krogsgaard-Larsen et al., Acta chem. Scand. B32, 327-334 (1978) in saturated methanolic hydrochloric acid was stirred for 17h at RT and evaporated in vacuo. The residue was dissolved in aqueous sodium hydroxide (4N) and extracted with
 15 ether. The combined organic phases were dried (MgSO₄), filtered and evaporated in vacuo. The residue was dissolved in ethanol and a solution of oxalic acid in ethanol was added. Crystallization from ether gave the title compound. M.P. 184-185 °C.

b. (RS)-5-Methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

20 The compound was synthesized as described in example 17 using (RS)-3-methoxycarbonyl-5-methyl-1,2,5,6-tetrahydropyridiniumoxalate and pentanamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively.
 M.P. 189-191 °C.

25 EXAMPLE 14(RS)-1,6-Dimethyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

30 The compound was synthesized as described in example 17 using 1,6-dimethyl-3-ethoxycarbonyl-1,2,5,6-tetrahydropyridinium oxalate (Bishop, Z. Naturforsch. 25b, 1249-1251 (1970)) and pentanamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively. M.P. 141-142 °C.

EXAMPLE 1535 1-Methyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

0.182ml (2.0mmol) of cyclopropylcarboxylic acid chloride was added to a solution of 200mg (1.29mmol) 1-methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime in 8 ml DMF.
 40 The mixture was stirred at 55 °C for 4 h and evaporated in vacuo. The residue was refluxed with acetic acid for 16 hours. After evaporation in vacuo the residue was dissolved in 5ml 4N aqueous sodium hydroxide and was extracted with ether. The combined ether phases were dried with MgSO₄ and evaporated in vacuo. The residue contained both the title compound and 1-methyl-3-cyano-1,2,5,6-tetrahydropyridine. After chromatographic separations, the title compound crystallized with oxalic acid from ethanol and ether.
 45 M.P. 172-173 °C.

EXAMPLE 1650 1-Methyl-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 15 using 1-methyl-1,2,5,6-tetrahydropyridin-4-carboxamide oxime instead of 1-methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime.
 M.P. 173-174 °C.

55 EXAMPLE 171-methyl-3-(3-(2-thienyl)-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using 2-thiophen carboxamide oxime instead of methoxymethyl carboxamide oxime. Crystallization gave the title compound in 46% yield. M.P. 149-150 °C.

5 EXAMPLE 18

1-methyl-3-(3-octyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using nonanamide oxime instead of methoxymethyl carboxamide oxime. Crystallization gave the title compound in 19% yield. M.P. 122-123 °C.

EXAMPLE 19

1-methyl-3-(3-pentyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using hexanamide oxime instead of methoxymethyl carboxamide oxime. Crystallization gave the title compound in 40% yield. M.P. 149-150 °C.

EXAMPLE 20

1-methyl-3-(3-heptyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using octanamide oxime instead of methoxymethyl carboxamide oxime. Crystallization gave the title compound in 33% yield. M.P. 94-95 °C.

EXAMPLE 21

3-(3-isopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 9 using norarecoline, HCl instead of arecoline, HBr. M.P. 199-200 °C.

EXAMPLE 22

3-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 9 using norarecoline, HCl and benzamide oxime instead of arecoline, HBr and isopropyl carboxamide oxime, respectively. M.P. 208-209 °C.

EXAMPLE 23

3-(3-(2-thienyl)-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example using norarecoline, HCl and 2-thiophen carboxamide oxime instead of arecoline, HBr and isopropyl carboxamide oxime, respectively. M.P. 199-200 °C.

EXAMPLE 24

1-methyl-4-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

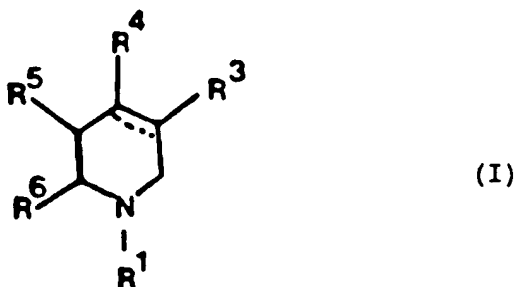
Benzamide oxime (440 mg; 5,0 mmol), dicyclohexylcarbodiimide (1030 mg; 5,0 mmol) and 4-carboxy-1-methyl-1,2,5,6-tetrahydropyridinium chloride (886 mg; 5,0 mmol) were mixed in distilled DMF. The mixture was stirred at 60 °C for 1 1/2 h and evaporated in vacuo. To the residue was added water (50 ml) and the mixture was extracted with toluene (3x75 ml). pH was adjusted to 10 by means of 4N NaOH and extracted with toluene (3x100 ml). The combined extracts were dried (Na₂SO₄) and evaporated in vacuo. Upon dissolving the residue in ethanol (99.9%) (5 ml) a solution of oxalic acid (360 mg; 4,0 mmol) in ethanol

(99,9%) (5 ml) was added. Crystallization gave the title compound. M.P. 172-173°C.

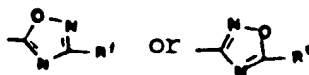
Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

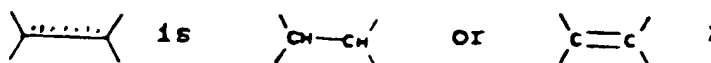
1. Piperidine compounds of the general formula I



wherein
at least one of R³, R⁴ and R⁵ is



and the others independently are H or C₁₋₆-alkyl,
wherein R' is C₃₋₈-alkyl, phenyl, thienyl, cyclopropyl, or C₁₋₃-alkoxymethyl; and
R¹ and R⁶ independently are H or C₁₋₆-alkyl



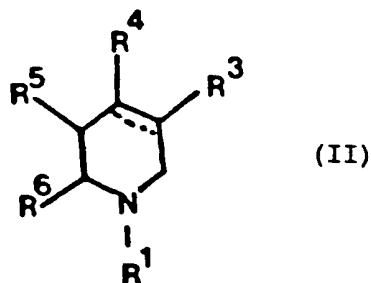
and salts thereof with a pharmaceutically-acceptable acid.

2. The compound of claim 1 which is 1-methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine.
3. The compound of claim 1 which is 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine of a salt thereof with a pharmaceutically acceptable acid.
4. The compound of claim 1 which is 1-methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
5. The compound of claim 1 which is 3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
6. The compound of claim 1 which is 1-methyl-3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
7. The compound of claim 1 which is 3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
8. A process for preparing a compound of claim 1 comprising

a) reacting a reactive derivative of a compound of the general formula II

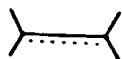
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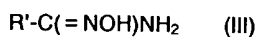
wherein R¹, R⁶, and



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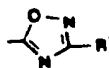
have the meanings defined above and
wherein one of R³, R⁴ and R⁵ is CO₂H or a reactive derivative thereof, such as an ester, and the
others independently are H or C₁₋₆-alkyl, with a compound having the general formula III

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wherein R' has the meaning defined above to form a compound of the general formula I, wherein
one of R³, R⁴ and R⁵ is

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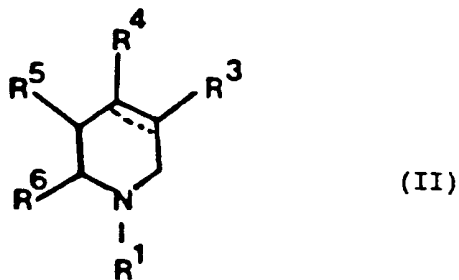


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wherein R' has the meaning defined above,
b) reacting a compound of the general formula II

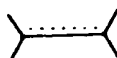
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wherein R¹, R⁶ and



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have the meanings defined above and
wherein one of R³, R⁴ and R⁵ is CN and the others independently are H or C₁₋₆-alkyl, with NH₂OH

to form a compound having the general formula II wherein one of R^3 , R^4 and R^5 is $C(=NOH)NH_2$ and the others independently are H or C_{1-6} -alkyl and reacting this compound with $R'-COCl$ or $(R'-CO)_2O$ to form a compound of formula I, wherein one of R^3 , R^4 and R^5 is

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wherein R' has the meaning defined above.

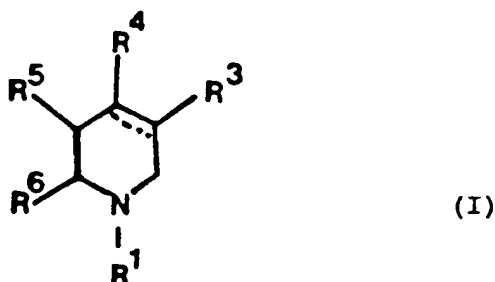
9. A pharmaceutical composition comprising an effective amount of a compound of any of claims 1 to 7 together with a pharmaceutically-acceptable carrier or diluent.
10. The pharmaceutical composition according to claim 9 which is in the form of an oral dosage unit containing 1-100 mg of the active compound.
11. Use of a compound of any of claims 1 to 7 for the preparation of a medicament useful in stimulating the cognitive functions of the forebrain and hippocampus of mammals, including humans, and therefore in treating Alzheimer's disease in the same.

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Claims for the following Contracting States : AT, ES

1. A process for preparing piperidine compounds of the general formula I

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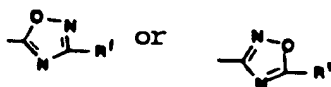


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wherein
at least one of R^3 , R^4 and R^5 is

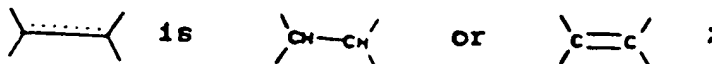
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and the others independently are H or C_{1-6} -alkyl,
wherein R' is C_{3-8} -alkyl, phenyl, thienyl, cyclopropyl or C_{1-3} -alkoxymethyl; and
 R^1 and R^6 independently are H or C_{1-6} -alkyl

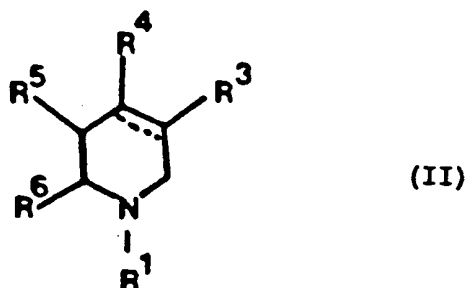
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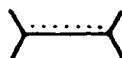
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and salts thereof with a pharmaceutically-acceptable acid, comprising

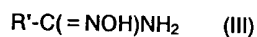
a) reacting a reactive derivative of a compound of the general formula II



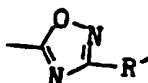
15 wherein R¹, R⁶ and



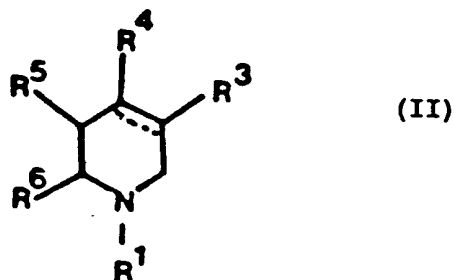
have the meanings defined above and
wherein one of R³, R⁴ and R⁵ is CO₂H or a reactive derivative thereof, such as an ester, and the
others independently are H or C₁₋₆-alkyl, with a compound of the general formula III



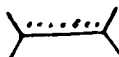
wherein R' has the meaning defined above to form a compound of the general formula I, wherein
one of R³, R⁴ and R⁵ is



35 wherein R' has the meaning defined above,
b) reacting a compound of the general formula II



50 wherein R¹, R⁶ and



have the meanings defined above

and

wherein one of R³, R⁴ and R⁵ is CN and the other independently are H or C₁₋₆-alkyl, with NH₂OH to form a compound having the general formula II wherein one of R³, R⁴ and R⁵ is C(=NOH)NH₂ and the others independently are H or C₁₋₆-alkyl,

and reacting this compound with R¹-COCl or (R¹-CO)₂O to form a compound of formula I, wherein one of R³, R⁴, and R⁵ is

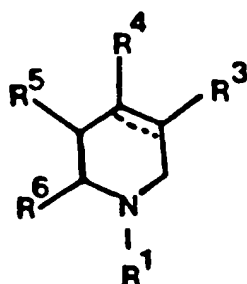


wherein R¹ has the meaning defined above.

2. The process of claim 1 wherein the prepared compound is 1-methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine.
3. The process of claim 1 wherein the prepared compound is 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
4. The process of claim 1 wherein the prepared compound is 1-methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
5. The process of claim 1 wherein the prepared compound is 3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
6. The process of claim 1 wherein the prepared compound is 1-methyl-3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
7. The process of claim 1 wherein the prepared compound is 3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
8. A process for preparing a pharmaceutical composition comprising formulating an amount of a compound prepared according to any of claims 1 to 7 together with a pharmaceutically-acceptable carrier or diluent.
9. The process of claim 8 wherein the composition is in the form of an oral dosage unit containing 1-100 mg of the active compound.
10. The use of a compound prepared according to any of claims 1 to 7 for the preparation of a medicament useful in stimulating the cognitive functions of the forebrain and hippocampus of mammals, including humans, and therefore in treating Alzheimer's disease in the same.

Claims for the following Contracting State : GR

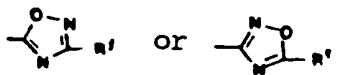
1. Piperidine compounds of the general formula I



(I)

wherein
at least one of R³, R⁴ and R⁵ is

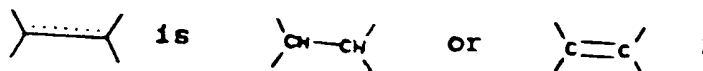
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and the others independently are H or C₁₋₆-alkyl,
wherein R' is C₃₋₈-alkyl, phenyl, thienyl, cyclopropyl, or C₁₋₃-alkoxymethyl; and
R¹ and R⁶ independently are H or C₁₋₆-alkyl

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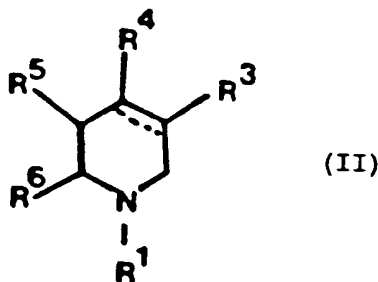
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and salts thereof with a pharmaceutically-acceptable acid.

2. The compound of claim 1 which is 1-methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine.
3. The compound of claim 1 which is 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
4. The compound of claim 1 which is 1-methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
5. The compound of claim 1 which is 3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
6. The compound of claim 1 which is 1-methyl-3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
7. The compound of claim 1 which is 3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine or a salt thereof with a pharmaceutically acceptable acid.
8. A process for preparing a compound of claim 1 comprising
 - a) reacting a reactive derivative of a compound of the general formula II

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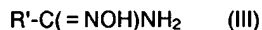
(II)

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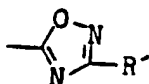
wherein R¹, R⁵, and



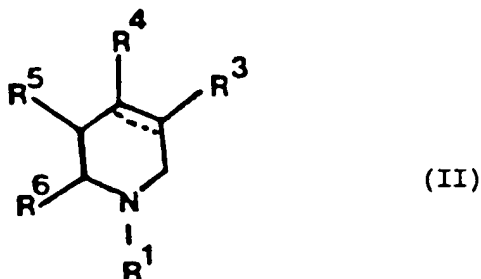
5 have the meanings defined above and
wherein one of R^3 , R^4 and R^5 is CO_2H or a reactive derivative thereof, such as an ester, and the
others independently are H or C_{1-6} -alkyl, with a compound having the general formula III



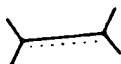
wherein R' has the meaning defined above to form a compound of the general formula I, wherein
one of R^3 , R^4 and R^5 is



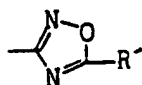
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20 wherein R' has the meaning defined above,
b) reacting a compound of the general formula II



35 wherein R^1 , R^5 and



40 have the meanings defined above and
wherein one of R^3 , R^4 and R^5 is CN and the others independently are H or C_{1-6} -alkyl, with NH_2OH
45 to form a compound having the general formula II wherein one of R^3 , R^4 and R^5 is C(=NOH)NH_2
and the others independently are H or C_{1-6} -alkyl and reacting this compound with $\text{R}'\text{-COCl}$ or $(\text{R}'\text{-CO})_2\text{O}$ to form a compound of formula I, wherein one of R^3 , R^4 and R^5 is



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55 wherein R has the meaning defined above.

9. A process for preparing a pharmaceutical composition comprising formulating an amount of a compound according to any of claims 1 to 7 together with a pharmaceutically-acceptable carrier or diluent.

10. The process of claim 9 wherein the composition is in the form of an oral dosage unit containing 1-100 mg of the active compound.

Patentansprüche

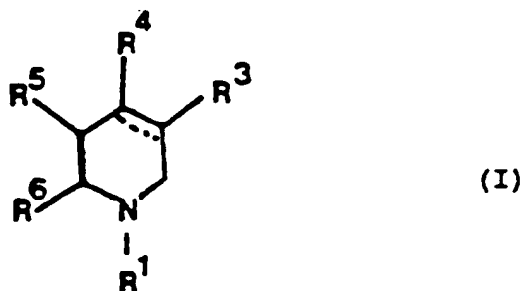
5 **Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Piperidinverbindungen der allgemeinen Formel I

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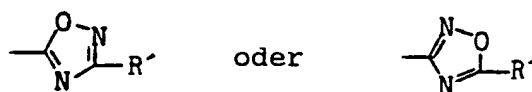
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worin wenigstens einer der Substituenten R³, R⁴ und R⁵

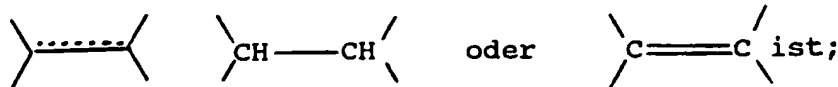
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ist und die anderen unabhängig voneinander H oder C₁₋₆-Alkyl sind, worin R' C₃₋₈-Alkyl, Phenyl, Thienyl, Cyclopropyl oder C₁₋₃-Alkoxymethyl ist; und R¹ und R⁵ unabhängig voneinander H oder C₁₋₆-Alkyl sind;

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und Salze davon mit einer pharmazeutisch annehmbaren Säure.

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2. Verbindung nach Anspruch 1, welche 1-Methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin ist.
3. Verbindung nach Anspruch 1, welche 3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
4. Verbindung nach Anspruch 1, welche 1-Methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
5. Verbindung nach Anspruch 1, welche 3-(3-Butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
6. Verbindung nach Anspruch 1, welche 1-Methyl-3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
7. Verbindung nach Anspruch 1, welche 3-(3-Methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin

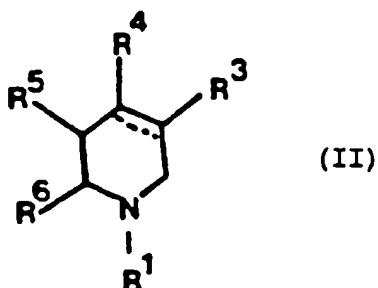
oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.

8. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, umfassend
a) die Umsetzung eines reaktiven Derivats einer Verbindung der allgemeinen Formel II

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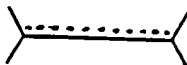
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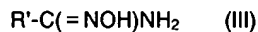
worin R¹, R⁶ und

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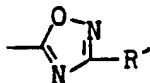
die vorstehend angegebene Bedeutung besitzen und einer der Substituenten R³, R⁴ und R⁵ CO₂H oder ein reaktives Derivat davon, wie ein Ester, ist und die anderen unabhängig voneinander H oder C₁-₆-Alkyl sind, mit einer Verbindung der allgemeinen Formel III



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worin R' die vorstehend angegebene Bedeutung besitzt, zur Bildung einer Verbindung der allgemeinen Formel I, worin einer der Substituenten R³, R⁴ und R⁵

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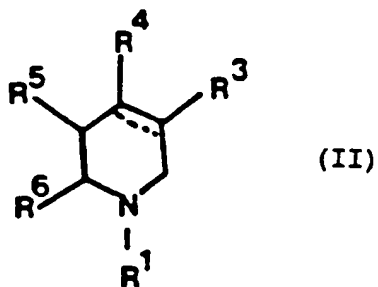


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worin R' die vorstehend angegebene Bedeutung besitzt, ist,
b) die Umsetzung einer Verbindung der allgemeinen Formel II

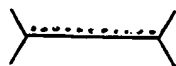
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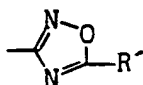


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worin R¹, R⁶ und



die vorstehend angegebene Bedeutung besitzen und einer der Substituenten R^3 , R^4 und R^5 CN ist und die anderen unabhängig voneinander H oder C_{1-6} -Alkyl sind, mit NH_2OH zur Bildung einer Verbindung der allgemeinen Formel II, worin einer der Substituenten R^3 , R^4 und R^5 $C(=NOH)NH_2$ ist und die anderen unabhängig voneinander H oder C_{1-6} -Alkyl sind, und die Umsetzung dieser Verbindung mit R^1-COCl oder $(R^1-CO)_2O$ zur Bildung einer Verbindung der Formel I, worin einer der Substituenten R^3 , R^4 und R^5

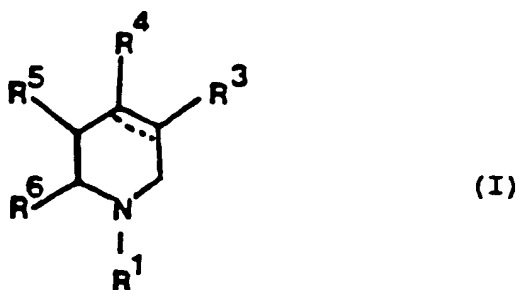


worin R' die vorstehend angegebene Bedeutung besitzt, ist.

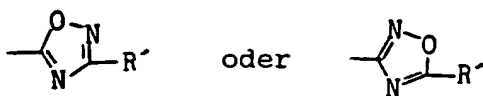
9. Pharmazeutische Zusammensetzung, umfassend eine wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 7 zusammen mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.
10. Pharmazeutische Zusammensetzung nach Anspruch 9, welche in Form einer oralen Dosierungseinheit, enthaltend 1 bis 100 mg der aktiven Verbindung, ist.
11. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Medikaments, das zur Stimulation bzw. Reizung der Erkenntnisfunktionen des Vorderhirns und Hippocampus von Säugern, einschließlich Menschen, und deshalb zur Behandlung der Alzheimer-Krankheit geeignet ist.

Patentansprüche für folgende Vertragsstaaten : AT, ES

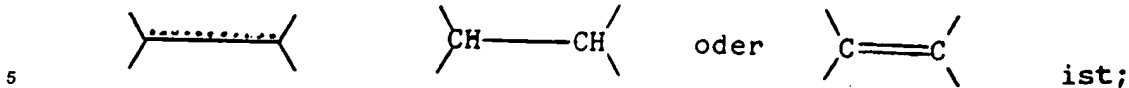
1. Verfahren zur Herstellung von Piperidinverbindungen der allgemeinen Formel I



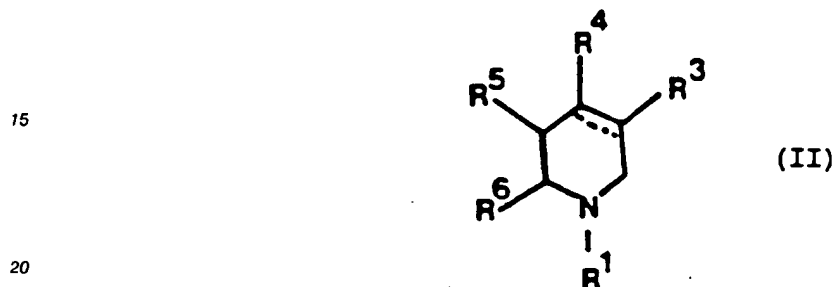
worin wenigstens einer der Substituenten R^3 , R^4 und R^5



ist und die anderen unabhängig voneinander H oder C_{1-6} -Alkyl sind, worin R' C_{3-8} -Alkyl, Phenyl, Thienyl, Cyclopropyl oder C_{1-3} -Alkoxyethyl ist; und R^1 und R^6 unabhängig voneinander H oder C_{1-6} -Alkyl sind;



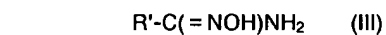
und Salzen davon mit einer pharmazeutisch annehmbaren Säure, umfassend
a) die Umsetzung eines reaktiven Derivats einer Verbindung der allgemeinen Formel II



worin R¹, R⁶ und



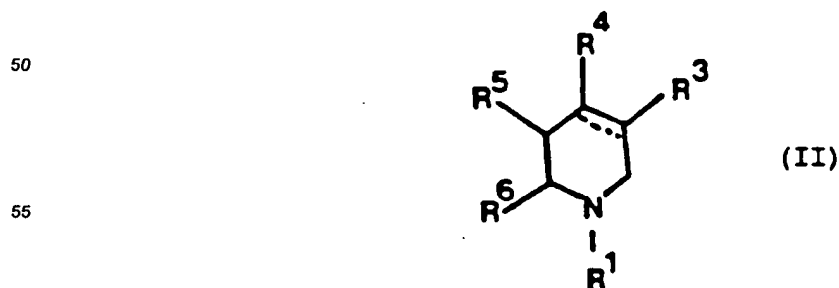
30 die vorstehend angegebene Bedeutung besitzen und einer der Substituenten R³, R⁴ und R⁵ CO₂H oder ein reaktives Derivat davon, wie ein Ester, ist und die anderen unabhängig voneinander H oder C₁₋₆-Alkyl sind, mit einer Verbindung der allgemeinen Formel III



worin R' die vorstehend angegebene Bedeutung besitzt, zur Bildung einer Verbindung der allgemeinen Formel I, worin einer der Substituenten R³, R⁴ und R⁵

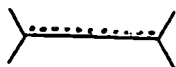


45 worin R' die vorstehend angegebene Bedeutung besitzt, ist,
b) die Umsetzung einer Verbindung der allgemeinen Formel II



worin R¹, R⁶ und

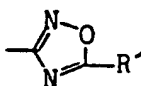
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10

die vorstehend angegebene Bedeutung besitzen und einer der Substituenten R³, R⁴ und R⁵ CN ist und die anderen unabhängig voneinander H oder C₁₋₆-Alkyl sind, mit NH₂OH zur Bildung einer Verbindung der allgemeinen Formel II, worin einer der Substituenten R³, R⁴ und R⁵ C(=NOH)NH₂ ist und die anderen unabhängig voneinander H oder C₁₋₆-Alkyl sind, und die Umsetzung dieser Verbindung mit R'-COCl oder (R'-CO)₂O zur Bildung einer Verbindung der Formel I, worin einer der Substituenten R³, R⁴ und R⁵

15



20

worin R' die vorstehend angegebene Bedeutung besitzt, ist.

25

2. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 1-Methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin ist.

30

3. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.

4. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 1-Methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.

5. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 3-(3-Butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.

35

6. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 1-Methyl-3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.

40

7. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 3-(3-Methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.

8. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das Formulieren einer Menge einer Verbindung, hergestellt nach einem der Ansprüche 1 bis 7, zusammen mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.

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9. Verfahren nach Anspruch 8, worin die Zusammensetzung in Form einer oralen Dosierungseinheit, enthaltend 1 bis 100 mg der aktiven Verbindung, ist.

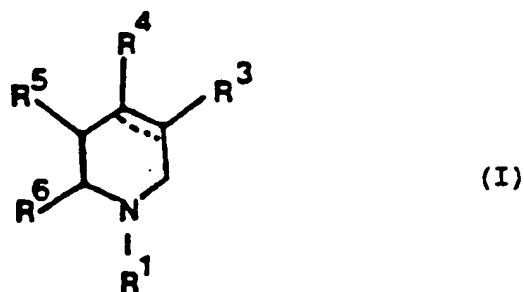
50

10. Verwendung einer Verbindung, hergestellt nach einem der Ansprüche 1 bis 7, zur Herstellung eines Medikaments, das zur Stimulation bzw. Reizung der Erkenntnisfunktionen des Vorderhirns und Hippocampus von Säugern, einschließlich Menschen, und deshalb zur Behandlung der Alzheimer Krankheit geeignet ist.

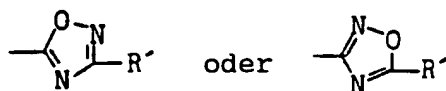
Patentansprüche für folgenden Vertragsstaat : GR

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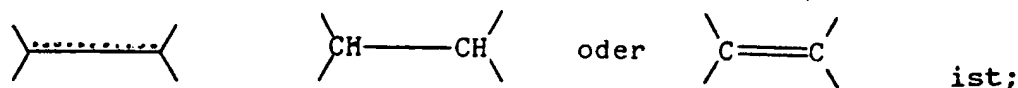
1. Piperidinverbindungen der allgemeinen Formel I



15 worin wenigstens einer der Substituenten R³, R⁴ und R⁵

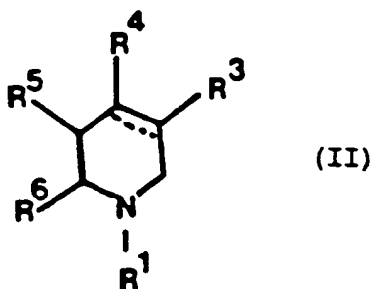


25 ist und die anderen unabhängig voneinander H oder C₁₋₆-Alkyl sind, worin R' C₃₋₈-Alkyl, Phenyl, Thienyl, Cyclopropyl oder C₁₋₃-Alkoxyethyl ist; und R¹ und R⁶ unabhängig voneinander H oder C₁₋₆-Alkyl sind;

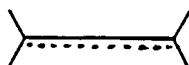


und Salze davon mit einer pharmazeutisch annehmbaren Säure.

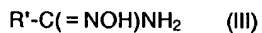
- 35 2. Verbindung nach Anspruch 1, welche 1-Methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin ist.
- 40 3. Verbindung nach Anspruch 1, welche 3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
4. Verbindung nach Anspruch 1, welche 1-Methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
- 45 5. Verbindung nach Anspruch 1, welche 3-(3-Butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
6. Verbindung nach Anspruch 1, welche 1-Methyl-3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
- 50 7. Verbindung nach Anspruch 1, welche 3-(3-Methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridin oder ein Salz davon mit einer pharmazeutisch annehmbaren Säure ist.
8. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, umfassend
- a) die Umsetzung eines reaktiven Derivats einer Verbindung der allgemeinen Formel II
- 55



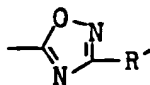
15 worin R¹, R⁶ und



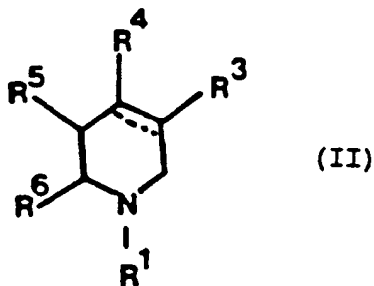
20 die vorstehend angegebene Bedeutung besitzen und einer der Substituenten R³, R⁴ und R⁵ CO₂H oder ein reaktives Derivat davon, wie ein Ester, ist und die anderen unabhängig voneinander H oder C₁-₆-Alkyl sind, mit einer Verbindung der allgemeinen Formel III



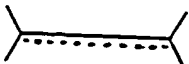
worin R' die vorstehend angegebene Bedeutung besitzt, zur Bildung einer Verbindung der allgemeinen Formel I, worin einer der Substituenten R³, R⁴ und R⁵



35 worin R' die vorstehend angegebene Bedeutung besitzt, ist,
b) die Umsetzung einer Verbindung der allgemeinen Formel II

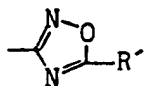


50 worin R¹, R⁶ und



55 die vorstehend angegebene Bedeutung besitzen und einer der Substituenten R³, R⁴ und R⁵ CN ist

und die anderen unabhängig voneinander H oder C₁₋₆-Alkyl sind,
mit NH₂OH zur Bildung einer Verbindung der allgemeinen Formel II, worin einer der Substituenten
R³, R⁴ und R⁵ C(=NOH)NH₂ ist und die anderen unabhängig voneinander H oder C₁₋₆-Alkyl sind,
und die Umsetzung dieser Verbindung mit R'-COCl oder (R'-CO)₂O zur Bildung einer Verbindung
der Formel I, worin einer der Substituenten R³, R⁴ und R⁵



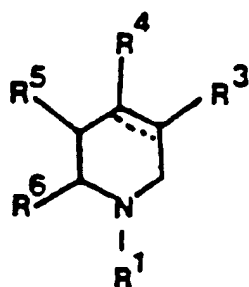
worin R' die vorstehend angegebene Bedeutung besitzt, ist.

9. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das Formulieren einer Menge einer Verbindung nach einem der Ansprüche 1 bis 7, zusammen mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.
10. Verfahren nach Anspruch 9, worin die Zusammensetzung in Form einer oralen Dosierungseinheit, enthaltend 1 bis 100 mg der aktiven Verbindung, ist.

Revendications

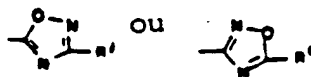
Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composés de pipéridine de formule générale I



(I)

où au moins l'un parmi R³, R⁴ et R⁵ est



et les autres sont indépendamment H ou un alkyle C₁₋₆, où R' est un alkyle C₃₋₈, un phényle, un thiényle, un cyclopropyle, ou un alkoxy méthyle C₁₋₃ ; et
R¹ et R⁶ indépendamment sont H ou un alkyle C₁₋₆

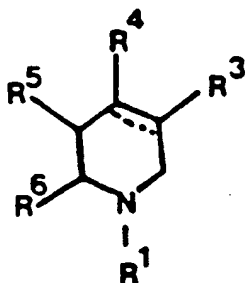
>.....< est >CH—CH< ou >C—C< ;

et leurs sels avec un acide acceptable en pharmacie.

2. Composé de la revendication 1 qui est du 1-méthyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine.
3. Composé de la revendication 1 qui est du 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyri-

dine ou l'un de ses sels avec un acide acceptable en pharmacie.

4. Composé de la revendication 1 qui est du 1-méthyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
5. Composé de la revendication 1 qui est du 3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
6. Composé de la revendication 1 qui est du 1-méthyl-3-(3-méthoxyméthyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
7. Composé de la revendication 1 qui est du 3-(3-méthoxyméthyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
8. Procédé de préparation d'un composé de la revendication 1 comprenant
 - a) la réaction d'un dérivé réactif d'un composé de formule générale II



(II)

où les définitions de R¹, R⁶, et

><

sont identiques à ci-dessus et

où l'un parmi R³, R⁴ et R⁵ est CO₂H ou l'un de ses dérivés réactifs, tel qu'un ester, et les autres sont indépendamment H ou un alkyle C₁₋₆, avec un composé de formule générale III

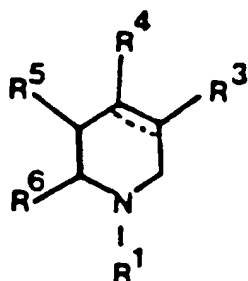
R'-C(=NOH)NH₂ (III)

où la définition de R' est identique à ci-dessus pour former un composé de formule générale I, où l'un parmi R³, R⁴ et R⁵ est



où la définition de R' est identique à ci-dessus,

b) la réaction d'un composé de formule générale II



(II)

où les définitions de R¹, R⁵ et

> <

sont identiques à ci-dessus et

où l'un parmi R³, R⁴ et R⁵ est CN et les autres sont indépendamment H ou un alkyle C₁-₆, avec NH₂OH pour former un composé de formule générale II où l'un parmi R³, R⁴ et R⁵ est C(=NOH)-NH₂ et les autres sont indépendamment H ou un alkyle C₁-₆ et la réaction de ce composé avec R'-COCl ou (R'-CO)₂O pour former un composé de formule I, où l'un Parmi R³, R⁴ et R⁵ est



où la définition de R' est identique à ci-dessus.

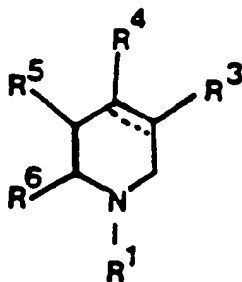
9. Composition pharmaceutique comprenant une quantité efficace d'un composé de l'une quelconque des revendications 1 à 7 ainsi qu'un véhicule ou un diluant acceptables en pharmacie.

10. Composition pharmaceutique selon la revendication 9 qui est sous la forme d'une unité de prise orale contenant de 1 à 100 mg du composé actif.

11. Utilisation d'un composé de l'une quelconque des revendications 1 à 7 pour la préparation d'un médicament servant à stimuler les fonctions cognitives du cerveau antérieur et de l'hippocampe des mammifères, y compris les humains, et servant par conséquent à traiter la maladie d'Alzheimer chez ces derniers.

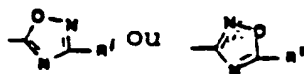
Revendications pour les Etats contractants suivants : AT, ES

1. Procédé de préparation de composés de pipéridine de formule générale I



(I)

où au moins l'un parmi R³, R⁴ et R⁵ est



5

et les autres sont indépendamment H ou un alkyle C_{1-6} , où R' est un alkyle C_{3-8} , un phényle, un thiényle, un cyclopropyle, ou un alkoxy méthyle C_{1-3} ; et R^1 et R^6 indépendamment sont H ou un alkyle C_{1-6}

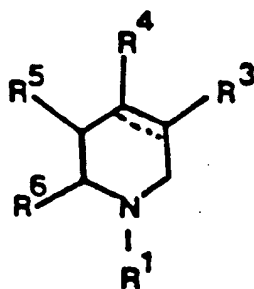
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et leurs sels avec un acide acceptable en pharmacie, comprenant

15

a) la réaction d'un dérivé réactif d'un composé de formule générale II

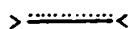


(II)

25

où les définitions de R^1 , R^6 , et

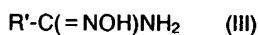
30



sont identiques à ci-dessus et

35

où l'un parmi R^3 , R^4 et R^5 est CO_2H ou l'un de ses dérivés réactifs, tel qu'un ester, et les autres sont indépendamment H ou un alkyle C_{1-6} , avec un composé de formule générale III



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où la définition de R' est identique à ci-dessus pour former un composé de formule générale I, où l'un parmi R^3 , R^4 et R^5 est



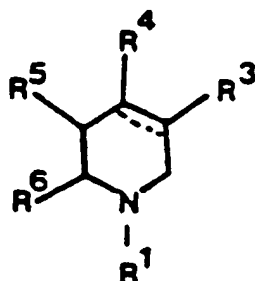
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où la définition de R' est identique à ci-dessus,

b) la réaction d'un composé de formule générale II

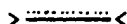
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(II)

où les définitions de R¹, R⁶ et



sont identiques à ci-dessus et

où l'un parmi R³, R⁴ et R⁵ est CN et les autres sont indépendamment H ou un alkyle C₁₋₆, avec NH₂OH pour former un composé de formule générale II où l'un parmi R³, R⁴ et R⁵ est C(=NOH)-NH₂ et les autres sont indépendamment H ou un alkyle C₁₋₆, et la réaction de ce composé avec R'-COCl ou (R'-CO)₂O pour former un composé de formule I, où l'un parmi R³, R⁴ et R⁵ est



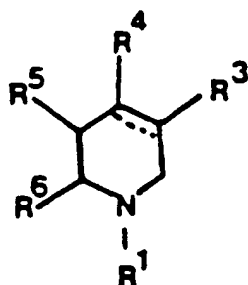
où la définition de R' est identique à ci-dessus.

2. Procédé de la revendication 1 dans lequel le composé préparé est du 1-méthyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine.
3. Procédé de la revendication 1 dans lequel le composé préparé est du 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
4. Procédé de la revendication 1 dans lequel le composé préparé est du 1-méthyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
5. Procédé de la revendication 1 dans lequel le composé préparé est du 3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
6. Procédé de la revendication 1 dans lequel le composé préparé est du 1-méthyl-3-(3-méthoxyméthyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
7. Procédé de la revendication 1 dans lequel le composé préparé est du 3-(3-méthoxyméthyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.
8. Procédé de préparation d'une composition pharmaceutique comprenant la formulation d'une quantité d'un composé préparé selon l'une quelconque des revendications 1 à 7 ainsi qu'un véhicule ou un diluant acceptables en pharmacie.
9. Procédé de la revendication 8 dans lequel la composition est sous la forme d'une unité de prise orale contenant de 1 à 100 mg du composé actif.
10. Utilisation d'un composé préparé selon l'une quelconque des revendications 1 à 7 pour la préparation d'un médicament servant à stimuler les fonctions cognitives du cerveau antérieur et de l'hippocampe

des mammifères, y compris les humains, et servant par conséquent à traiter la maladie d'Alzheimer chez ces derniers.

Revendications pour l'Etat contractant suivant : GR

1. Composés de pipéridine de formule générale I



(I)

où au moins l'un parmi R³, R⁴ et R⁵ est



et les autres sont indépendamment H ou un alkyle C₁₋₆, où R¹ est un alkyle C₃₋₈, un phényle, un thiényl, un cyclopropyle, ou un alkoxy méthyle C₁₋₃ ; et R¹ et R⁶ indépendamment sont H ou un alkyle C₁₋₆

>.....< est >CH—CH< ou >C=C< ;

et leurs sels avec un acide acceptable en pharmacie.

2. Composé de la revendication 1 qui est du 1-méthyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine.

3. Composé de la revendication 1 qui est du 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.

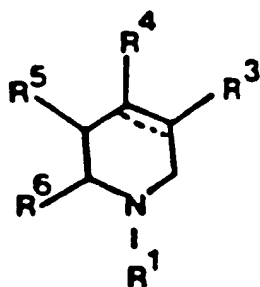
4. Composé de la revendication 1 qui est du 1-méthyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.

5. Composé de la revendication 1 qui est du 3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.

6. Composé de la revendication 1 qui est du 1-méthyl-3-(3-méthoxyméthyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.

7. Composé de la revendication 1 qui est du 3-(3-méthoxyméthyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tétrahydropyridine ou l'un de ses sels avec un acide acceptable en pharmacie.

8. Procédé de préparation d'un composé de la revendication 1 comprenant
a) la réaction d'un dérivé réactif d'un composé de formule générale II



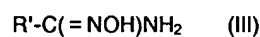
(II)

où les définitions de R^1 , R^6 , et

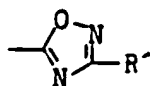


sont identiques à ci-dessus et

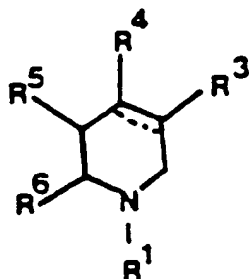
où l'un parmi R^3 , R^4 et R^5 est CO_2H ou l'un de ses dérivés réactifs, tel qu'un ester, et les autres sont indépendamment H ou un alkyle C_{1-6} , avec un composé de formule générale III



où la définition de R' est identique à ci-dessus pour former un composé de formule générale I, où l'un parmi R^3 , R^4 et R^5 est



où la définition de R' est identique à ci-dessus,
b) la réaction d'un composé de formule générale II



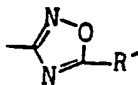
(II)

où les définitions de R^1 , R^6 et



sont identiques à ci-dessus et

où l'un parmi R^3 , R^4 et R^5 est CN et les autres sont indépendamment H ou un alkyle C_{1-6} , avec NH_2OH pour former un composé de formule générale II où l'un parmi R^3 , R^4 et R^5 est $\text{C}(=\text{NOH})\text{-NH}_2$ et les autres sont indépendamment H ou un alkyle C_{1-6} et la réaction de ce composé avec $\text{R}'\text{-COCl}$ ou $(\text{R}'\text{-CO})_2\text{O}$ pour former un composé de formule I, où l'un parmi R^3 , R^4 et R^5 est



5 où la définition de R est identique à ci-dessus.

9. Procédé de préparation d'une composition pharmaceutique comprenant la formulation d'une quantité de composé selon l'une quelconque des revendications 1 à 7 ainsi qu'un véhicule ou un diluant acceptables en pharmacie.

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10. Procédé de la revendication 9 dans lequel la composition est sous la forme d'une unité de prise orale contenant de 1 à 100 mg du composé actif.

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